REMARKS

These remarks are in response to the Office Action mailed September 15, 2004. Claims 1, 9, 10 and 12 have been amended to define Applicant's invention. Applicants ask for consideration and allowance of the pending claims as amended.

Objection Maintained

Regarding paragraph 5, Applicants will submit the required formal drawings at a future date.

Rejection under 35 § USC 112

In paragraph 10 of the 9/15/04 Office Action, the Examiner rejected claim 9 as being indefinite, maintaining the rejection from the Office Action of 02/18/04, paragraph 18b. Applicants have amended claim 9, as suggested by the Examiner, to define that SEQ ID No. 7 is a nucleotide sequence. Having made this amendment, Applicants respectfully request the withdrawal of the § 112 rejection.

Rejection under 35 § USC 102(b)

Claims 1 and 3 are not anticipated under 35 § USC 102 (b) by Hoyer *et al.* (1998) because Hoyer *et al.* does not disclose every element of Applicant's invention as claimed. To summarize, the Office Action of 9/15/04 states that the claimed N-terminal fragment does not exclude Hoyer's (1998) N-terminal protein fragment; that Hoyer *et al.* (1998) teaches the claimed composition comprising a biocompatible carrier; that the functional limitation, *i.e.*, production of an effective immune response is considered as an inherent property inseparable from the prior art N-terminal protein fragment; and that Applicants have not established that

Hoyer's (1998) isolated and purified 433 amino acid-long 65kDa N terminal fragment contained in PBS is incapable of producing an effective immune response in a patient. Applicants respectfully traverse.

Anticipation: "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California* 814 F.2d 628, 631, (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.,* 868 F.2d 1226 (Fed. Cir. 1989). (See MPEP § 2131)

Taking Examiner's remarks in order:

In paragraph 11 (p. 4, line 8) of the 9/15/04 Office Action, Examiner states, "Applicants' acknowledgment that Hoyer *et al.* (1998) taught a 433 amino acid-long N-terminal fragment of ALS1 protein of *Candida albicans* dissolved in PBS has been noted." Applicants respectfully disagree, because this misstates Applicants position. This is also different from what the Examiner states earlier in the same Office action (p. 3, ¶4, line 2) in summarizing Applicants' position, "Applicants acknowledge that the ALS1 N-terminal fragment was dissolved in and dialyzed against PBS, but only as part of a mixture of other peptides." It is important to keep the fact clear that Hoyer *et al.* (1998) had a mixture of proteins dialyzed against PBS that was only enriched in ALS1 N-terminal fragment, but did not have an isolated and purified preparation of N-terminal fragment of ALS1 protein. Further, Hoyer *et al.* (1998) did not use even this enriched preparation as immunogen. Therefore, the claimed element of "isolated and purified" is not disclosed by Hoyer *et al.* (1998) and the § 102 rejection cannot be maintained.

In the same paragraph (p. 4, line 10), Examiner states, "More importantly, Applicants' admission that Hoyer *et al.* (1998) used a mixture of four 10-mer peptides derived from conserved regions of ALS1 as antigen to produce anti-ALS1 antiserum has been noted." Again, Applicants respectfully disagree. What was stated by Applicants was that Hoyer *et al.* (1998) used conserved regions common to all ALS proteins, not just ALS1. A mixture of four 10-mers was used as antigen; and one of these was not specific for ALS protein.

Examiner states (p. 4, ¶2, line 1), " ...instant claims 1 and 3, as amended currently, do not define the claimed N-terminal fragment by its structure or amino acid composition, i.e., SEQ ID number." Claim one has been amended to define the claimed N-terminal fragment.

For the Hoyer *et al.* (1998) prior art product to anticipate the applicant's claimed pharmaceutical composition, the Hoyer product must meet each and every element, either expressly or inherently, as set forth in the claims. As noted above, Claim one recites "... isolated and purified N-terminal fragment...." Hoyer *et al.* (1998) does not have an isolated and purified preparation of N-terminal ALS1 protein fragment. At the point in Hoyer's procedure where the prior art product is dialyzed against PBS, Hoyer *et al.* had a mixture of ALS1p N-terminal fragment from Candida albicans and proteins from *Saccharomyces cerevisiae*, which is an enriched preparation of the ALS1 fragment, but not an isolated and purified one. Because the polypeptide of interest in Hoyer *et al.* is associated with a mixture of other proteins, the polypeptide of interest is not "isolated and purified" as claimed. Even if the protein of interest is from one species, and the remaining proteins in the mixture are from another species, as is the case with secreted recombinant proteins, the standard of "isolated and purified" is not met for the protein of interest.

The preparation of both isolated and purified preparations of a selected protein as antigen to focus the elicited immune response specifically on the selected antigen requires more than a mere enrichment. A "purified" and "isolated" composition is readily distinguished from the heterogonous mixture of Hoyer *et al.* (1998), especially where the element of pharmaceutical composition is recited. In such compositions, it is necessary to avoid undesirable immunogenic cross reactions that can result in unacceptable side effects. To use merely an enriched mixture of proteins as described by Hoyer *et al.* (1998) as immunogen is not an acceptable procedure, and on its face, would not be a pharmaceutical composition as claimed.

The Examiner states (9/15/04 OA; p. 6:18) that at the stage where the Hoyer *et al.* (1998) prior art product is dialyzed against PBS that Hoyer's N-terminal ALS1 fragment is "sufficiently purified" for inclusion in a pharmaceutical composition. This statement lacks any supporting scientific evidence, and is speculative, at best. The standard under § 102 requires a clear and unequivocal disclosure of each element of the claim. Applicants request that the Examiner support this statement (p. 6:18) with a showing.

Although PBS is a recognized pharmaceutical accepted carrier, the pending claims require a biocompatible carrier and an isolated and purified N-terminal fragment of ALS1p as immunogen. At the point in the procedure when Hoyer *et al.* (1998) had the N-terminal fragment of ALS1p dialyzing against PBS, the ALS1 N-terminal fragment was not isolated and purified, but was merely enriched. To stretch the open-endedness of the word "comprising" to imply that a preparation of "isolated and purified" ALS1 N-terminal fragment could contain undefined proteins and still produce the desired specific, effective immune response is neither scientifically accurate nor therapeutically responsible. It is highly questionable whether a

mixture of yeast proteins and ALS1 protein fragment would give the same antigen response as that of a purified preparation of ALS1p and a suitable carrier. Hoyer *et al.* (1998) did not use the prior art product as immunogen. Applicants, on the other hand, have demonstrated the efficiency and usefulness of a pharmaceutical composition of an acceptable biocompatible carrier and an isolated and purified preparation of the N-terminal fragment of ALS1 protein.

At paragraph 11 of the 9/15/04 Office Action, Examiner states that pending claims 1 and 3 do not define the claimed N-terminal fragment by its structure or amino acid composition. Applicants have amended claim 1 to include the appropriate SEQ ID number, which also pertains to dependent claim 3. Dependent claim 9 recites a specific nucleotide listing.

Continuing at paragraph 11 of the 9/15/04 Office Action, Examiner states, "Hoyer *et al.* (1998) do teach the claimed composition comprising a biocompatible carrier. The functional limitation, i.e., production of an effective immune response, on which the prior art reference is allegedly silent, is considered as an inherent property inseparable from the prior art N-terminal protein fragment." This limitation is included to distinguish a generalized immune response to a mixture containing an enriched N-terminal fragment, or the potential inherent ability of a N-fragment of ALS1 to generate an antigenic response. If the enriched preparation of Hoyer *et al.* (1998) were used as an antigen, the immune response as claimed would not result. The response will not be the specific immune response already demonstrated by Applicants for therapeutic treatment to prevent binding of *Candida* to endothelial cells. The presence of various unspecified yeast proteins in Hoyer *et al.* (1998)'s composition distinguishes the immune response that results from use of the composition claimed.

Continuing at paragraph 11 of the 9/15/04 Office Action (p. 4, ¶2, line 13), Examiner states, "Applicants have not established that Hoyer's (1998) **isolated and purified** (emphasis added) 433 amino acid-long 65kDa N terminal fragment contained in PBS is incapable of producing an effective immune response n (sic) a patient." Applicants respectfully traverse. This is not an accurate statement. Again, it is important to keep the facts clear. Hoyer *et al.* (1998) did not have an isolated and purified preparation of the N-terminal fragment of ALS1 protein despite several purification steps, but only a partially purified preparation enriched in the ALS1 protein N-terminal fragment in a mixture of undisclosed yeast proteins.

It is well known in the art of protein chemistry that protein purification is difficult and arduous. Applicants simplified the purification of the N-terminal fragment of ALS1 protein by attaching a 6-His tag, a known acceptable procedure, to enhance the ease of protein separation. Hoyer *et al.* (1998) did not use such a device, but relied on standard techniques, such as ammonium sulfate fractionation and centrifugation, steps which are far less precise.

Hoyer *et al.* (1998) clearly state that the four 10-mer peptides were chosen because they were common for all ALS proteins. The function of Applicants' claimed composition is to elicit an effect immune response specific to an ALS1 protein N-terminal fragment. The use of Hoyer's (1998) prior art product of a mixture of four 10-mer peptides, each of which is common to all ALS proteins (and one which is non-specific), does not sufficiently establish the effective immune response to ALS1 protein N-terminal fragment as recited in Applicants' claims. The 10 mers are each peptides synthesized from the predicted amino acid sequence. They would not demonstrate the surface complexity of the native structure of the N terminal fragment of the ALS1 protein, which is needed to elicit the effective immune response claimed by Applicants.

Further, the mixture of four 10 mer peptides is not a even specific immunogen for all ALS proteins, since at least one of the peptides is found in a totally unrelated protein.

Claims 9 and 12 have been amended to recite that the N-terminal fragment of ALS1 protein is encoded by nucleotides 52-1296 of SEQ ID No. 7. This is exactly what is stated in the specification on p. 18, lines 14-16. Applicants submit that since the language of the amended claim is supported by the specification, there is no new matter inserted.

The typographical misspelling of "agluttinin" is corrected. Once this spelling correction is made for claim 10, dependent claims 11 and 12 depend appropriately. Applicants respectfully request withdrawal of this indefiniteness rejection.

(section 14, p. 8, line 1) Examiner states that new claims 10 and 11 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hoyer *et al.* (1998) as evidenced by Harlow *et al.* (1988). In this section, Examiner again blurs important distinctions and repeats arguments made earlier in this 9/15/04 Office Action. Applicants will respond respectfully again, however, to each argument, to keep important distinctions clear.

Examiner states (p. 8, ¶2, line 1), "Hoyer's (1998) taught a composition, which comprises the **purified** (emphasis added) N-terminal domain of an **adhesion** (emphasis added) protein, Als1p, of Candida albicans dissolved in PBS, i.e., a biocompatible carrier for injection or infusion (see pages 5334, 5336 and 5337)." Applicants submit the Hoyer *et al.* (1998) prior art product in PBS is not purified, only enriched, because when the N-terminal fragment of ALS1 is dialylzed against PBS, it is clearly part of a mixture of yeast proteins. Hoyer's later steps of electrophoresis, electroblotting onto a membrane and N-terminal amino acid sequencing do not constitute the "biocompatible carrier for injection or infusion, and an isolated and purified N-

terminal fragment of agglutinin like sequences (ALS1) cell surface adhesion protein (SEQ ID No. 7) obtained from Candida albicans..." as recited in Applicants' Claim 1. For the Hoyer *et al.* (1998) prior art product, when the ALS1 N-terminal fragment was present with PBS, it was not "isolated and purified " because unspecified yeast proteins were present. In the further steps required for amino acid sequencing, the Hoyer prior art product was not disclosed as being mixed with PBS, nor was the Hoyer *et al.* (1998) preparation used as an antigen. Finally, Applicants emphasize that the function of ALS1 as an adhesin protein was not described by Hoyer *et al.* in 1998, but by Fu et al. (2002). As of 1998, the function of the ALS1 protein as an adhesin protein had not been established.

The Office Action states that Hoyer *et al.* (1998) anticipates claim 1 of the application under 102 (b). The issue then is to compare the elements of Claim 1 with that of Hoyer *et al.* (1998) to determine if all elements of claim 1 are represented in Hoyer *et al.* (1998).

Claim 1	Hoyer *et al.* (1998)	Reason why Hoyer *et al.* (1998) does not anticipate Claim 1
1. A **pharmaceutical composition** comprising:	Hoyer does not disclose a pharmaceutical composition.	**--A mixture of ALS1 and carrier S.c. protein would not be a suitable pharmaceutical composition for producing a specific immune response with ALS1 being the antigen of interest.**
a biocompatible carrier for injection or infusion, and	An extract dialyzed against PBS.	--PBS is a biocompatible carrier.
an isolated and purified	Hoyer does not disclose further purification or use of ALS1, other than Western blotting solely for identification purposes.	**--Hoyer does not have an isolated and purified ALS1 protein.** Instead, Hoyer has a **mixture** of recombinant ALS1 and S.c. carrier proteins, which is dialyzed against PBS.
N-terminal fragment of agglutinin like sequences (ALS1) cell surface adhesion protein (SEQ ID No. 7)	--Hoyer discloses the N-terminal portion of the ALS1 protein from *Candida albicans* as a single band on an electrophoresis gel.	
obtained from *Candida albicans*, wherein	--As antigen, Hoyer used 4,10 mers of a common area to all ALS proteins.	**--A mixture of ALS1 and carrier S.c. protein would not produce the effective immune response as described in the Application.** --4, 10 mers would not distinguish those ALS proteins that bind endothelium from those ALS proteins that do not bind endothelium.
the composition produces an effective immune response in a patient.		

Hoyer *et al.* (1998) never disclose a composition that is both isolated and purified. Hoyer *et al.* had a heterologous mixture of recombinant ALS1 in *Saccharomyces cerevisiae* cells. Hoyer's preparation dialyzed against PBS, however, contains ALS1 and *S. cerevisiae* proteins,

all of which were precipitated by ammonium sulfate. If this mixed heterologous preparation were to be used as antigen, one of skill in the art would expect antibodies to be raised against all of the proteins, including the *S. cerevisiae* proteins. In fact, during their experiments, Applicants realized that *S. cerevisiae* carrier cells could be expected to cause an antigenic response, and went to great lengths to remove cross-reactivity with *S. cerevisiae* antigens by pre-absorption. As Applicants stated:

> "...unfractionated antisera will undoubtedly contain large amounts of antibodies directed towards antigens on *Saccharomyces cerevisiae* carrier cells. Many of these anti-*Saccharomyces* antibodies would likely bind to *C. albicans* and make interpretation of the results impossible. (specification, p. 21, line 9)

Other than electrophoresis, Hoyer *et al.* (1998) does not provide methodology for the separation of ALS1 protein from *S. cerevisiae* proteins and so does not disclose the **isolated and purified** ALS1 polypeptide as claimed.

It is not clear what the scientific results would be if the dialyzed ammonium sulfate preparation of Hoyer *et al.* (1998) were to be used to induce an immune response. Applicants submit it is speculative at best to state that a similar immune responses would be obtained, when such different preparations are used as antigen. It is understood by scientists in Immunology that it is not trivial to obtain a specific antigenic response, particularly for vaccine purposes, and most especially for therapeutic application in animals. Applicants, therefore, emphasize the requirement in claims for "an isolated and purified" ALS1 protein as antigen to induce an immune response. The Hoyer *et al.* (1998) prior art product, therefore, does not expressly or inherently possess the characteristics claimed by Applicants.

While Hoyer *et al.* (1998) did have a single electrophoretic band at 65kDa, Hoyer did not disclose any further experimentation or use for this band, other than a probable identity of ALS1. It is known by those skilled in the art of protein separation, however, that having a single electrophoretic band, in itself, is not solely indicative of purification of a single protein. A rigorous protein separation traditionally involves a combination of experimental results, such as chromatographic purity, electrophoresis migration under denaturing and non-denaturing conditions, peptide analysis, N-terminal determination, etc. A single band may not represent a purified protein, especially when heterologous mixtures are involved. Until the possibility that another protein(s) with similar electrophoretic characteristics co-migrates at 65kDA, this makes it difficult to predict immune response for a "purified" protein isolated from an electrophoresis gel.

The Office Action (9/15/04) states that Applicants have not established that Hoyer's (1998) isolated and purified 433 amino acid-long 65kDa N terminal fragment contained in PBS is incapable of producing an effective immune response in a patient. However, this is not the appropriate standard. Applicants do not have the burden to prove "incapability" of the prior Art to produce the claimed invention. Instead, the prior art reference must disclose the claimed invention in "as complete detail" as the claims. See Richardson supra.

To the extent the Examiner relies on inherent anticipation, practice of the prior art reference must produce the exact composition recited in the claims *each and every* time it is performed – it is *not* sufficient that there is a mere probability or possibility that the patented result will occur. *Id.* ("Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is

not sufficient"). To inherently anticipate, the patented compound must be "necessarily present" in the reference. *See Glaxo Group Ltd. v. Apotex, Inc.*, No. 03-1575, 2004 U.S. App. LEXIS 15489, at *22 (Fed. Cir. July 27, 2004) (*citing Schering Corp. v. Geneva Pharms, Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003)).

The specific requirement of the inherent anticipation doctrine that the prior art produce the claimed invention each and every time it is practiced is particularly important in this case. The law is clear that evidence that the prior art process does not produce the patented compound every time it is performed, precludes inherent anticipation. *See Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047 (Fed. Cir. 1995), *see also 3M Unitek Corp. v. Ormco Co.*, 1042, 1048 (C.D. Cal. 2000).

Clearly, this standard is not met by Hoyer *et al.* (1998) in the present case. The Office Action (9/15/04) states that the PBS dialysate of the ammonium sulfate precipitation meets the claimed product in that: (a) the N-terminal portion of Als1p is isolated from the cellular mass of the microorganism; and (b) the N-terminal portion of Als1p is purified in that it is free of other antigens of *Candida albicans* since it is recombinantly expressed in a heterologous host. However, this MIXTURE of proteins cannot be an express or inherent anticipation of the isolated and purified ALS1 N-terminal fragment of the claims.

If a telephone call would further prosecution of this case, the Examiner is invited to call the undersigned patent agent at (949) 567-6700, extension 7798.

The Applicant's attorney of record hereby authorizes the Commissioner to charge any amounts due in the above-identified application to Orrick, Herrington & Sutcliffe's Deposit Account No. **150665** and to credit any overpayments to said Deposit Account No. **150665**.

Respectfully submitted,

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